DESCRIPTION

USE OF VASOPRESSIN ANTAGONISTS

The invention relates to the use of at least one vasopressin receptor antagonist or mixtures thereof.

As is known, vasopressin (VP) is a peptide hormone from the posterior lobe of the hypophysis. As a result of its antidiuretic action it is also known as antidiuretin or antidiuretic hormone (ADH). The hormone form occurring in humans and many mammals is a cyclic peptide of nine amino acids with a disulphide bridge, in which arginine is in the eight-position. This form is correspondingly also known as arginine vasopressin (AVP).

As stated, the influence of vasopressin in water diuresis in the kidneys, namely the antidiuretic action which it produces, is physiologically particularly important. Vasopressin makes the collecting tubules in the kidney permeable to water and in this way permits the re-resorption of water in the kidneys and consequently the concentration of the urine. The epithelial tissues of the collecting tubules react to the presence of vasopressin. The hormone supplied from the blood side of the epithelial cells is bound to specific receptors and by means of intracellular cAMP (second messenger cyclic adenosine-3',5-monophosphate) stimulates the increase in water permeability. The fundamental mechanism can be conceived in such a way that water channel-forming glycoproteins are formed in the so-called chief cells. In the case of the chief cells of the collecting tubules of the kidney, this glycoprotein is the hitherto solely detected aquaporine-2 there. It is initially stored in small vesicles in the cell interior and in the presence of vasopressin at the receptor is incorporated into the apical cell membrane. As a result the hormonally regulated water entry into the cell is permitted.

Vasopressin receptors which bring about a cAMP-dependent water channel regulation in the epithelial cells of the collecting tubules in the kidney are known as V_2 receptors.

Thus, in the epithelial cells of the collecting tubules of the kidney, vasopressin has a water-re-resorbing action. This can be inhibited by vasopressin receptor antagonists. Correspondingly said antagonists in the kidney

oppose the action of vasopressin and consequently increase the urine flow whilst simultaneously diluting the urine.

In conjunction with the antidiuretic action of vasopressin already vasopressin receptor antagonists are known. These can be peptidic or non-peptidic substances. In connection with the peptidic substances reference is made to the publications of M. Manning and W.H. Sawyer in J. Lab. Clin. Med. 114, 617-632 (1989) and F.A. Laszlo et al. in Pharmacol. Rev., 43, 73-108 (1991). Descriptions of non-peptidic substances appear in Y. Yamamura et al. in Br. J. Pharmacol. 105, 787-791 (1992) and C. Serradeil-Le Gal et al. in J. Clin. Invest., 98 (12), 2729-2738 (1996). All these substances are investigated and used in connection with the antidiuretic action of the vasopressin.

Findings and investigations up to now concerning disturbances and illnesses of the inner ear cannot be brought into accord with the above-described findings concerning the antidiuretic action of vasopressin and the inhibition of this action by antagonists. This particularly also applies to the so-called endolymphatic hydrops in the inner ear, in which there is an endolymph fluid excess in the endolymphatic area of the inner ear. This endolympathic hydrops can be linked with an overproduction or outflow or discharge disturbance of the endolymph, particularly in the so-called endolymphatic sac (Saccus endolymphaticus). Although the existence of vasopressin has been detected in the inner ear, a use of vasopressin antagonists cannot be considered as a result of the existing findings concerning the water-re-resorbing action of vasopressin. In the case of an increased liquid volume in the inner ear, which can trigger illness symptoms, the known action of vasopressin would be desired. This action would be inhibited by the use of the antagonist.

It has now surprisingly been found that in the inner ear, particularly in the epithelium of cells, which include the endolymph, the water permeability can be restored and improved by the use of vasopressin receptor antagonists. As a result of this unexpected, opposing action of the antagonist compared with its action in the kidney, the use of such substances or their mixtures for the treatment of disturbances or illnesses to the inner ear is made

possible.

Thus, the problem of the invention of making available active ingredients for the treatment of disturbances or illnesses in the inner ear, is solved by the use according to claim 1. Preferred developments are given in the dependent claims 2 to 16. The content of all these claims is hereby made by reference into part of the content of the description.

According to the invention, at least one vasopressin receptor antagonist or mixtures thereof can be used for treatment of disturbances or illnesses of the inner ear. This in particular also covers the use for producing a corresponding medicament or a corresponding pharmaceutical composition and the antagonist can optionally be used in the form of its pharmaceutically acceptable salts and optionally mixed with a pharmaceutically acceptable carrier or diluent.

The receptor antagonists used according to the invention are preferably those which interact with one of the aforementioned V_2 receptors. According to the present state of knowledge these V_2 receptors are the ones which are mainly linked with the antidiuretic action of vasopressin.

The disturbance or illness of the inner ear which is to be treated with the use according to the invention is preferably associated with one of the symptoms vertigo (vestibular disorders), impairment of hearing, tinnitus aurium or a pressure feeling in the ear. The symptoms vertigo, impairment of hearing or tinnitus are particularly stressed. In the use according to the invention one of these symptoms can occur alone, but there can also be a random combination of two or three symptoms or also the occurrence of all three or four symptoms are typical in the case of inner ear disturbances.

The hearing impairment symptom can in particular occur as so-called deep sound hearing impairment, preferably as fluctuating deep sound hearing impairment.

The inner ear disturbances or illnesses treatable through the use according to the invention can, according to the present state of knowledge, frequently

and preferably be linked with a so-called hydrops, particularly an endolymphatic hydrops. As is known a hydrops is a fluid accumulation or fluid collection in the body, particularly in the cavities present therein. In the case of the aforementioned endolymphatic hydrops it is a fluid excess of the so-called endolymph. This fluid excess can be attributed to an overproduction or an outflow disturbance of the endolymph, particularly in the so-called endolymphatic sac. Endolymphatic hydrops leads to an increased pressure and a volume increase in the space in which the endolymph is located. As with this is associated a modified deflectibility of the sensory hairs, which are responsible for hearing and vestibular sense, said symptoms, particularly vertigo, impairment of hearing and tinnitus, can be explained with an endolymphatic hydrops.

Among the treatable disturbances or illnesses particular reference is made to Menière's disease, which is normally associated with the symptoms vertigo, impairment of hearing and tinnitus aurium. There can be numerous influences acting as triggers for Menière's disease such as e.g. stress, infections, tumours, immunological or neurogenic disturbances, etc. In the present case Menière's disease is to be understood as a collective term for disturbances in which the corresponding symptoms can occur with different intensities, such as e.g. as vestibular Menière's disease. Another possible application is Lermoyez disease. Preferably disturbances/illnesses of the inner ear can be treatable, which manifest themselves in deep sound hearing impairment. Corresponding deep sound hearing impairments frequently also arise following inflammatory illnesses, such as insidious middle ear inflammation or syphilis, in the case of toxic influences or as delayed hydrops syndrome, or also as a consequence of venous stasis or vascular disturbances of the inner ear. All disturbances/illnesses of the inner ear, which in addition to those indicated hereinbefore can also be linked with outflow disturbances of the endolymph in the endolymphatic sac are possibly suitable for the use of the present invention.

According to the invention it is possible to use known or also further novel vasopressin receptor antagonists, particularly vasopressin-V_2-receptor antagonists. These substances, like vasopressin, can be peptide compounds, which in the same way as vasopressin interact with the receptor. Such peptide

compounds are e.g. disclosed in the aforementioned publication of M. Manning and W.H. Sawyer. These can in particular be comparatively easily accessible linear peptides and in particular it is possible to use the peptide propionyl-D-Tyr(Et)-Phe-Val-Asn-Abu-Pro-Arg-Arg-NH_2. The components of the reproduced peptide sequence have the standard meaning in biochemistry and Abu is α-L-aminobutyric acid. A selection of linear peptide compoundsin principle usable as vasopressin receptor antagonists, including the particularly stressed compound, appear in the publication of M. Manning et al in Int. J. Peptide Protein Res., 32, 455-467 (1988). The compound reproduced above with its peptide sequence is marketed by BACHEM Feinchemikalien AG, Bubendorf, Switzerland, under product No. H-9400.

It is fundamentally also possible to use non-peptidic receptor antagonists for vasopressin and these are preferably non-peptidic organic substances, which once again are preferably synthetically produced. In the case of the hitherto known organic substances these can be benzazepin derivatives, such as are e.g. described in EP-A1-514667. Particular reference is made to the substance 5-dimethylamino-1-{4-(2-methylbenzoylamino)-benzoyl}-2,3,4,5-tetrahydro-1H-benzazepin, described under the name OPC-31260 in the publication of Y. Yamamura et al. in Br. J. Pharmacol. 105, 787-791 (1992). The content of this publication is by reference made into part of the content of the present description. Other possible non-peptidic organic substances are indole derivatives, as are known fundamentally from WO 93/15051, WO 95/18105 and EP-A1-645375. As a N-sulphonyl-2-oxoindole derivative, particular reference is made to 1-[4-(N-tert.-butyl carbamoyl)-2-methoxybenzene sulphonyl]-5-ethoxy-3-spiro-[4-(2-morpholinoethoxy)-cyclohexane]-indol-2-one fumarate described under the name SR 121463A in J. Clin. Invest. 98 (12), 2729-2738 (1996).

According to the invention it is preferable for the receptor antagonist to be orally and/or intravenously administrable. An oral administration possibility, as in the case of non-peptidic receptor antagonists compared with peptidic receptor antagonists for vasopressin, is particularly favourable, because this greatly facilitates administration possibilities to a patient.

The use according to the invention of vasopressin receptor antagonists can

fundamentally take place in random ways and the selected administration form can be adapted to the age, sex or other characteristics of the patient, the severity of the disturbances/illnesses and other parameters. When using oral administration it is e.g. possible to produce tablets, pills, solutions, suspensions, emulsions, granules or capsules. Conventional pharmaceutical carriers, diluents or conventional additives can be present. For intravenous administration the antagonists can be provided alone or together with conventional auxiliary fluids, such as e.g. glucose, amino acid solutions, etc. A preparation for intramuscular, subcutaneous or interperitoneal administration is optionally also possible. An administration is suppository form is also conceivable.

The dosage can fundamentally be freely selected as a function of the clinical picture and the conditioning of the patient. Conventionally use is made of quantities of 0.1 to 5o mg/kg of body weight and per day. Per dosage unit the receptor antagonist for vasopressin is conventionally contained in a quantity of approximately 10 to 1,000 mg per unit. In a formulation or a corresponding medicament provided for administration the receptor antagonist for vasopressin is preferably contained in a quantity of 1 to 75 wt.%. Within this range values between 5 and 50 wt.%, particularly 5 and 25 wt.% are preferred.

The use of a formulation prepared according to the invention or a corresponding medicament fundamentally takes place systemically, preference being given to the aforementioned oral route. In certain circumstances a local application in the direction of the inner ear is possible, if e.g. as a result of an operation an access to the inner ear can be made. Thus, the application of drainage following exposure of the endolymphatic sac is possible and then e.g. with the aid of a pump via a corresponding catheter the vasopressin receptor antagonist can be passed directly to the action location of a corresponding inner ear disturbance/illness.

The invention also covers a process for the treatment of disturbances or illnesses of the inner ear and which is characterized in that at least one vasopressin receptor antagonist or mixtures thereof is administered in a suitable quantity for the body of the animal or person being treated. In

connection with the individual features of such a process reference is specifically made to the text up to now of this description, in which in particular the treatable disturbances/illnesses and the usable receptor antagonists are defined.

The invention finally covers a pharmaceutical composition or a medicament for the treatment of disturbances or illnesses of the inner ear, which contains at least one vasopressin receptor antagonist or mixtures thereof. In connec tion with the individual features of such a composition or medicament, reference is once again made to the corresponding description text up to now.

The described features and further features of the invention can be gathered from the following description of preferred embodiments in conjunction with the subclaims and drawings. The individual features can be implemented singly or in the form of subcombinations.

In the drawings show:

Fig. 1 The position of Reissner's membrane in the cochlea in adult guinea pigs
- a without vasopressin addition
- b with chronic vasopressin addition
- c with acute vasopressin addition
- d with acute vasopressin addition (detail enlargement)

Fig. 2 Expression of
- a V_2 receptor and
- b aquaporin-2

in the epithelium of the endolymphatic sac in the inner ear of the rat

Fig. 3 Autoradiography of the human endolymphatic sac
- c in the epithelium with ^{125}I-vasopressin
- d control test in the presence of unlabelled vasopressin

Fig. 4 Organotypical culture of the endolymphatic sac of the rat

a overall radiogram

b infrared light microscopy

c SEM radiogram

d SEM radiogram (greater magnification)

Fig. 5 Membrane turnover in the culture according to fig. 4

a FITC-dextran-labelled endosomes in the absence of vasopressin

b FITC-dextran-labelled endosomes in the presence of vasopressin

c SEM radiogram in case a

d SEM radiogram in case b

e FITC-dextran-labelled endosomes in the presence of forskolin

f FITC-dextran-labelled endosomes in the presence of choleratoxin

g FITC-dextran-labelled endosomes in the presence of vasopressin and V_2 receptor antagonist H-9400.

Experiment 1

Guinea pigs with a normal Preyer reflex and weighing between 300 and 500 g were used for the investigation. For investigating the acute action of vasopressin Pitressin$^{(R)}$ (arginine-vasopressin AVP) from Sankyo, Japan was intraperitoneally injected (0.2 units/g). For histology the guinea pigs were killed two hours after the injection. For the chronic experiments 0.5 units/g of vasopressin were subcutaneously administered for 60 days once a day. For investigating the acute action use was made of 20 animals and for the investigation of the chronic action 10 animals. For comparison purposes in the case of the 10 control animals 0.2 ml of physiological common salt solution was intraperitoneally injected. The cochleae of all the test animals were embedded in celloidin and the mid-modiolar sections were dyed with hematoxylin/eosin (HE). As a result of the deflection of Reissner's membrane the presence of an endolymphatic hydrops was determined.

The results of experiment 1 are represented in fig. 1.

Fig. 1a shows that the Reissner's membrane indicated in exemplified manner by an arrow is not deflected in the control animals (n = 10) and

correspondingly there is no endolymphatic hydrops.

According to fig. 1b in the case of a test animal with chronic administration of vasopressin (n = 10) it is possible to detect a strong endolymphatic hydrops as a result of the pronounced displacement of Reissner's membrane. In the cochlear spiral, which corresponds to that marked with the arrow in fig. 1a, the Reissner's membrane is even in contact with the bony septum between spiral turns 3 and 4. Four of the ten test animals chronically treated with vasopressin had severe hydrops according to fig. 1b and three others had slight to moderate hydrops.

Fig. 1c shows a slight to moderate endolymphatic hydrops in a test animal following a single injection of vasopressin, i.e. acute treatment. At n = 20 eight of these twenty test animals had such slight to moderate hydrops. Fig. 1d shows the same case as fig. 1c, but with a higher magnification. As opposed to fig. 1b no contact with the bony septum is detectable, but there are clear protrusions of Reissner's membrane.

Thus, experiment 1 and the associated fig. 1 show that increased plasma values of vasopressin can give rise to an endolymphatic hydrops.

Experiment 2

Using the primers AQP2s, AQP2as, V2s and V2as PCR (polymerase-chain reaction) experiments were performed. The primers had the following nucleotide sequences:

AQP2s	GAT CGC CGT GGC CTT TGG TCT
AQP2as	AGG GAG CGG GCT GGA TTC AT
V2s	AGT GCT GGG GGC CCT AAT ACG
V2as	CAA ATC GGG CCC AGC AAT CAA ACA

The cDNAs of aquaporin-2 and the V_2 receptor were amplified by the use of the primer pairs AQP2s/AQP2as and V2s/V2as. The PCRs were performed in a total volume of 50 µl containing 5 µl of reverse transcriptase, in each case 0.8µM of primer, in each case 200 µM of dNTPs, an incubation buffer

(containing 1.5 mM $MgCl_2$ from Pharmacia) and 1.25 U of Taq polymerase (also from Pharmacia). Following a denaturation step of 7.5 min at 94°C at the start there were 40 cycles lasting 50 sec at 94°C, 50 sec at 55°C and 50 sec at 72°C and a ten minute stage at 72°C to the end. The expected product lengths were 428 bp and 419 bp. The PCR products were worked up in the usual way and detected by subcloning and sequencing.

As can be gathered from fig. 2, both V_2 receptor and aquaporin-2 were strongly expressed in the epithelium of the endolymphatic sac, whereas in other epithelia of the inner ear, also in contact with the endolymph, such a detection was unsuccessful.

According to fig. 2a in the inner ear of the rat the V_2 receptor could be detected both on the postnatal day 4 (p4) and in the grown rat (ad). Very weak bands were obtained in the endolymphatic sac on postnatal day 1 (p1), in the stria vascularis (StV), in the vestibular organ (V) or in Reissner's membrane (RM). According to fig. 2b the expression of aquaporin-2 was most clearly detectable in the grown endolymphatic sac on postnatal day 4, but it was not possible to detect any expression in the stria vascularis, the vestibular organ or Reissner's membrane.

Experiment 3

Human endolymphatic sac was obtained from six autopsies and two patients who had undergone operations with the authorization of relatives or the patients. Frozen sections (20 µm) were sectioned on a cryostat at -16°C, applied to gelatin-coated platelets and stored overnight in vacuo at 4°C. The tissue sections were incubated overnight at 4°C with ^{125}I-arginine-vasopressin in the absence (total binding) or presence of 10 µM of unlabelled arginine-vasopressin (unspecific binding), namely in ice cold 10 mM tris-HCl buffer (pH 7.4) containing 10 mg of $MgCl_2$, 0.5 mg/ml of bacitracin and 0.1% bovine serum albumin. The radio-labelled sections were coated with NTB-2 nuclear emulsion (Eastman Kodak) and prepared for light microscopic autoradiography. The coated plates were stored 3 to 8 days in the dark at 4°C. After developing and fixing the plates were dyed with hemotoxylin/eosin.

Fig. 3 shows the results of experiment 3. It is possible to see the specific binding of radioactive vasopressin in the human endolymphatic sac. The dots in fig. 3c show the binding of the vasopressin in the epithelium of the endolymphatic sac, whilst according to fig. 3d the same treatment in the presence of unlabelled vasopressin excludes an unspecific vasopressin binding in the sac.

Experiment 4

On postnatal day 4 rats were put to sleep using sodium pentobarbital (0.4 mg/gr body weight) and then decapitated. The temporal bones were immediately removed and transferred into cold (4°C) HEPES-buffered common salt solution with salt solution (HHBSS) adjusted with Hank's. The complete endolymphatic sac was separated from the temporal bone, opened at the corner of the distal sac part and inserted flat in a culture plate, which was coated with 20 µl of Cell Tek of Becton Dickinson Labware, USA, with a dilution of 1:5 and covered with 300 µl of culture medium. The culture medium consisted of minimum essential medium with D-valine, in order to suppress the growth of fibroblasts and which was supplemented with 10% foetal calf serum (FCS), 10 mM HEPES, 100 IU/ml penicillin and 2 mM glutamine. The cultures were kept in a 5% carbon dioxide atmosphere at 37°C for up to 5 days. The morphology of the culture was observed by infrared light microscopy. A detailed surface morphology of the epithelia was obtained by SEM (scanning electron microscopy). The cover slips of the explants were fixed for 120 min in 2.5% glutaraldehyde, 0.1 M sodium cacodylate buffer, re-fixed for 60 min in 1% osmium tetroxide, washed, dried, gold-coated according to a standard process and investigated in a Hitachi 500-SEM.

Fig. 4 shows the results of experiment 4.

Fig. 4a provides a survey of an endolymphatic sac after 4 days in the culture, proximal (PSP), intermediate (ISP) and distal (DSP) sac parts being shown. The structural analysis of the culture epithelium of the endolymphatic sac shown in fig. 4b and 4c shows a clear similarity with the native organ with mitochondria-rich and ribosome-rich cells of a typical configuration. Thus, the radiogram of the infrared light microscope shows individual cells in the

intermediate part and two cell types can differ on the basis of configuration and surface morphology. The polygonally shaped cells corresponding to the ribosome-rich cells (RRC) have a flat surface, whereas the round cells corresponding to the mitochondria-rich cells (MRC) have numerous microvilli projecting into the opening. This is also clearly visible from the SEM radiogram according to fig. 4c. The greater magnification according to fig. 4d additionally clearly shows the clathrin-coated pits of the luminal cell membrane in the RRC cells of the endolymphatic sac (cf. arrow).

Experiment 5

In a culture according to experiment 4 following 12 hours culturing of the endolymphatic sac in HHBSS (pH 7.3), which contained 1.0 mg/ml of fluorescein isothiocyanate (FITC)-dextran (from Sigma, Germany), incubation took place for approximately 10 min at 37°C. The endolymphatic sac was then washed with HHBSS and fixed for 20 min in PBS with 4% paraformaldehyde. Fluorescence and interference contrast images were recorded by an epifluorescence microscope (Olympus AX-70, Germany) with a standard FITC filter set (excitation: 485 $\pm$ 20 nm; emission: > 510 nm) and superimposed in order to render visible also the non-fluorescing cells and to discriminate the mitochondria-rich and ribosome-rich cells.

Subsequently vasopressin, forskolin, choleratoxin (all from Sigma, Germany) or V_2 receptor antagonist H-9400 (BACHEM, Switzerland) were added to the solutions together with the FITC dextran, namely in the quantities described herinafter.

Fig. 5 shows the results of experiment 5.

Thus, fig. 5a shows the endocytosis represented by the FITC dextran-labelled endosomes and observed in the culture of the endolymphatic sac in RRC and MRC in the absence of further substances, i.e. in a control experiment (n = 120). On adding 1 nM of vasopressin (n = 84) the membrane turnover in RRC is inhibited, i.e. no labelled endosomes are visible in RRC. Labelled endosomes are still observed in MRC. This means that in the endolymphatic sac the vasopressin (as opposed to the situation in the epithelium of the

collecting tubules of the kidney) inhibits the absorption of FITC dextran in ribosome-rich cells (RRC). Thus, in the example according to fig. 5b 10.5 ± 2.1 of 118.5 ± 2.8 cells reveal FITC dextran absorption (n = 20) compared with an untreated specimen according to the example of fig. 5a in which 90.5 ± 2.5 of 116.5 ± 2.4 cells revealed FITC dextran absorption (at n = 20).

The inhibitory effect of vasopressin on the membrane turnover is also demonstrated by the disappearance of the clathrin-coated pits from the apical cell surface of the ribosome-rich cells in accordance with the SEM radiograms of figs. 5c and 5d. Thus, under control conditions RRC revealed numerous coated pits (cf. arrow in fig. 5c), which were shown with a greater magnification in fig. 4d. The crossbar in fig. 5d represents a length of 1 um. Following a treatment with 1 mM of vasopressin according to fig. 5d almost no holes are visible, which reveals the internalization of the probably aquaporin-2-clustered clathrin.

As in the case of vasopressin, according to fig. 5e and 5f almost no endosomes were detected when using 50 µM of forskolin (n = 48) or 0.1 nM of choleratoxin (n = 36).

Just as surprising as the result of the experiment shown in fig. 5b is the test result according to fig. 5g, in which a simultaneous application of 10 nM of vasopressin and 10 nM of $\bar{V}_2$ receptor antagonist H-9400 cancelled out the vasopressin effect according to fig. 5b. The FITC dextran-filled endosomes are still present (test number n = 30).

The described FITC dextran tests make use of the known fact that the membrane turnover can be represented by FITC dextran and can be correlated with the water transport through the membrane. A high membrane turnover revealed by FITC dextran makes it possible to conclude that there is a high water transport. As the epithelium of the endolymphatic sac comprises almost exclusively RRC and MRC cells, the proof provided according to experiment 5 is valid for the complete endolymphatic sac and the supplying duct. The results are also in accordance with the fact that vasopressin is active on the RRC cells and consequently the effect of vasopressin or vasopressin antagonist can be detected there. The MRC cells are not active with vasopressin and

correspondingly reveal no effect according to experiment 5.

Due to the fact that the peptidic antagonist H-9400 used is a comparatively selective V_2 receptor antagonist, the test results constitute a strong indication that the vasopressin receptor at the endolymphatic sac of the inner ear is of the V_2 type. However, surprisingly the vasopressin in the inner ear clearly has a reverse action to that in the epithelial cells of the collecting tubule of the kidney. This explains the surprising result that the vasopressin receptor antagonist increases membrane turnover and consequently water transport as opposed to the known actions in the kidney and consequently a water-resorbing action is obtained through the use of the antagonist. This systematic finding makes the use according to the invention of the vasopressin receptor antagonist for the treatment of illnesses or disturbances of the inner ear, particularly those associated with a hydrops, such as an endolymphatic hydrops, possible. An antagonist action associated with a volume decrease on the luminal side, unlike the known action in the kidney, in the inner ear in the case of an overpressure or an excessive volume leads to a pressure and volume decrease. These are suitable for ameliorating or eliminating the symptoms, i.e. in particular vertigo, impairment of hearing and tinnitus. The use according to the invention can also have a prophylactic effect with such inner ear disturbances.